DETAILED ACTION

This office action is in response to applicant's request for continued examination filed on November 6, 2009.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Status of Claims

Claims 1- 12 are currently pending and are the subject of this office action.

Claims 7-12 were withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention/species, there being no allowable generic or linking claim. Election has been treated as an election without traverse in the reply filed on December 5, 2007.

Claims 1-6 are currently under examination.

Species being examined: PTK 787 as the 4-pyridylmethyl-phtalazine derivative of formula I.

Priority

The present application is a 371 of PCT/EP03/210578 filed on 09/23/2003, and claims priority to provisional application No. 60/413,176 filed on 09/24/2002.

Rejections and/or Objections and Response to Arguments

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated (Maintained Rejections and/or Objections) or newly applied (New Rejections and/or Objections, Necessitated by Amendment or New Rejections and/or Objections not Necessitated by Amendment). They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1) Claims 1-3 and 5 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Raza et. al. (Blood (2001) 98: 958-965, cited in prior office action) and Canepa et. al. (British Journal of Haematology (2001) 115:313-315, cited in prior office action) in view of Drevs et. al. (Cancer Research (2000) 60:4819-4824, cited in prior office action).

Claims 1-3 and 5 recite a method of treating myelodysplastic syndromes (MDS) comprising administering a therapeutically effective amount of PTK787 (species elected) to a warm blooded animal (human in claim 5) in need thereof.

For claims 1-3 and 5, Raza et. al. teach a method of treating MDS with thalidomide in humans(see abstract and introduction). Canepa et. al. further teach that thalidomide is a VEGF inhibitor (see page 313, left column, last line through right column, fourth line).

Neither Raza et. al. nor Canepa et. al. teach the treatment of MDS with PTK787. However, Drevs et. al. teach that PTK787 is an inhibitor of VEGF receptor (see abstract, line 5). Drevs et. al. also teach that PTK787 is used for the treatment of renal cancer in vivo in a murine model.

Since Raza et. al. teach a method of treating MDS with thalidomide (a VEGF inhibitor according to Canepa et. al.), and since Drevs et. al. teach that PTK787 is a VEGF inhibitor, at the time of the invention it would have been *prima facie* obvious for a person of ordinary skill in the art to substitute one functional equivalence (any VEGF inhibitor including thalidomide) for another (PTK787) with an expectation of success, since the prior art establishes that both function in similar manner, thus resulting in the practice of claims 1-3 and 5, with a reasonable expectation of success.

2) Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Raza et. al. (Blood (2001) 98: 958-965, cited in prior office action) and Canepa et. al. (British Journal of Haematology (2001) 115:313-315, cited in prior office action) in view of Drevs et. al. (Cancer Research (2000) 60:4819-4824, cited in prior office action) as applied to claims 1-3 and 5 above, and further view of Calabresi et. al. (US 6,429,224)

Claim 4 further limits claim 1, wherein the disease is resistant to conventional chemotherapy.

Raza et. al. and Canepa et. al. in view of Drevs et. al. teach all the limitations of claim 4, except for the disease being resistant to conventional therapy.

However, Calabresi et. al. teach that MDS cells can be resistant to drugs (see column 9, lines 26-27).

Since the prior art (Raza, Canepa and Drevs) teaches a method of treating MDS patients comprising administering a therapeutically effective amount of PTK787, and since Calabresi teaches that a subpopulation of those patients are resistant to conventional therapies, it would have been *prima facie* obvious at the time the invention was made to treat that specific subpopulation, with the motivation of finding a better treatment for MDS patients that are resistant to conventional therapies , thus resulting in the practice of claim 4 with a reasonable expectation of success.

3) Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Raza et. al. (Blood (2001) 98: 958-965, cited in prior office action) and Canepa et. al. (British Journal of Haematology (2001) 115:313-315, cited in prior office action) in view of Drevs et. al. (Cancer Research (2000) 60:4819-4824, cited in prior office action) as applied to claims 1-3 and 5 above, and further view of Goodman and Gilman's The Pharmacological Basis of Therapeutics (Tenth Edition (2001), McGraw Hill, pages 24-29).

Claim 6 further limits claim 1, wherein the total daily dosage of PTK787 is applied to the warm blooded animal by administration of two separate units comprising the same or different amounts of PTK787.

For claim 6, Drevs further teaches that PTK787 can be administered once daily (see page 4820, under administration of drugs). Drevs is silent regarding the number of units. However, Goodman and Gilman's teach that dosage regimen optimization is routine in the pharmaceutical art. For example on pages 27 and 28 under the heading: Individualizing dosage, the authors mention that: "A rational dosage regimen is based on knowledge of pharmacokinetic parameters (F, CL, Vss and t1/2) and some information about rates of absorption and distribution of the drug". They also teach: "Individualization of the dosage regimen to a particular patient is, therefore, critical for optimal therapy. The pharmacokinetic principles, described above, provide a basis for modifying the dosage regimen to obtain a desired degree of efficacy with a minimum of unacceptable adverse effects."

At the time of the invention, it would have been *prima facie* obvious for a person of ordinary skill in the art to further modify the dosages taught by Drevs, since dose regimen optimization is routine practice in the pharmaceutical art, with the motivation of determining the dose regimen for PTK787 required for optimal therapy for a particular patient, thus resulting in the practice of claim 6 with a reasonable expectation of success.

Response to Applicant's arguments related to the above rejection

Applicant's arguments have been fully considered but are not persuasive.

Applicant argues that:

The Examiner is referred to Applicants' remarks made in the Amendment After Final Rejection filed September 10, 2009, which are here incorporated by reference. In these remarks, Applicants argued that Raza et. al. teaches that thalidomide's cytoprotective and/or anticytokine properties, are believed to be the primary, basis for its utility in treating MDS.

In the Advisory Action dated September 18, 2009, the Examiner responds that Raza et al "indicates that the antiangiogenic activity of Thalidomide is as important as the cytoprotective and/or anticytokine activity for the treatment of MDS". However, a teaching of the equal importance of all of these properties el thalidomide for treating MDS would not suggest to the skilled artisan that MDS should be treated with an antiangiogenic compound that is not also known to possess cytoprotective and/or anticytokine properties. Therefore, combined disclosure of the references does not suggest the presently claimed invention.

Examiner's response:

Raza does not make any definitive statement regarding what is exactly that causes Thalidomide to be effective against MDS.

Raza teaches: "Attempts to suppress this excessive cytokine-mediated apoptosis in MDS with cytoprotective and/or anticytokine therapies have resulted in substantial improvements in the cytopenias of some MDS patients. The bone marrows of MDS patients also demonstrate markedly increased neo-angiogenesis and higher-than-

normal levels of vascular endothelial growth factor. Thalidomide was considered a potentially useful drug for MDS patients. It is an immune-modulatory agent with anticytokine activities and has antiangiogenic effects. Thalidomide has meaningful activity in multiple myeloma, even though the precise mechanism of its action remains unclear. On the basis of this rationale, a pilot study was conducted to test the efficacy of thalidomide in improving the ineffective hematopoiesis seen in patients with myelodysplastic syndromes" (see Introduction on page 958).

In other words, although Raza is teaching that Thalidomide has both: antiangiogenic and cytoprotective and/or anticytokine properties, Raza does not provide a definitive response as to which of these factors is the most important in the treatment of MDS, although it is clear that one or both might be influential. So the skilled in the art will be motivated to treat MDS with any compound that is either: antiangiogenic, cytoprotective, or both. In this case, the prior art (Drevs et. al.) teaches that PTK787, like Thalidomide, is a VEGF inhibitor and an antiangiogenic agent (see abstract), so the skilled in the art will be motivated to substitute one functional equivalence (any VEGF inhibitor/antiangiogenic compound including thalidomide) for another (PTK787) with an expectation of success, since the prior art establishes that both function in similar manner.

Conclusion

No claims are allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is (571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCOS SZNAIDMAN/
Examiner, Art Unit 1612
December 15, 2009.